Treatment of Chronic Myeloid Leukemia with Imatinib: A Study of 48 Cases in Burkina Faso

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Abstract

Introduction: The purpose of the study was to evaluate the management of patients treated with Imatinib for Chronic Myeloid Leukemia (CML) in the Department of Clinical Hematology of the Yalgado OUEDRAOGO University Hospital in Ouagadougou, Burkina Faso.

Patients and Methods: The study was a retrospective, descriptive study of records of patients with CML over 13 years. The diagnosis was based on testing for the Philadelphia chromosome and/or BCR-ABL transcript. The primary endpoint of the evaluation was survival time.

Results: 48 patients were collated. Patients' mean age at diagnosis was 40±13.47 (extreme ages are 13 and 80 years). The sex ratio was 1.52. Splenomegaly was prevalent (72.9%). The majority of patients were diagnosed in the chronic phase (81%). The calculated Sokal score showed high risk in 59.09% of the patients. Follow-up molecular biology on imatinib was performed in only six over 48 patients due to a lack of financial means. We found 92.34% survival in five years. The most common cause of death was severe anemia followed by acutization. We noted three cases of resistance out of 48 (6.25%) after the first three years of treatment.

Conclusion: CML affects people of all age groups. An early introduction of imatinib, the development of a well-organized hematology department, improved access to confirmatory CML testing and molecular biology to follow-up the residual disease will help to improve the poor prognosis and survival rate of our patients with chronic myeloid leukemia.

Keywords: Chronic Myeloid Leukemia; Philadelphia Chromosome; BCR-ABL Transcript; Imatini; Burkina Faso

Introduction

Chronic myeloid leukemia (CML) is a malignant hematologic disorder that falls in the group of myeloproliferative syndromes (or myeloproliferative neoplasms according to the WHO 2016 classification). It is defined by the presence of a chromosomal abnormality in the hematopoietic cells, known as the Philadelphia chromosome (Ph1). The Philadelphia chromosome is chromosome 22 derived from the balanced reciprocal translocation t (9, 22) (q34; q11). The chimeric protein, encoded by the BCR-ABL fusion transcript resulting from this rearrangement, has a constitutively deregulated tyrosine kinase activity and is directly responsible for the leukemic transformation. This protein has become the target of a tyrosine kinase inhibitor (TKI), Imatinib (an ATP-competitive inhibitor), whose significant therapeutic efficacy has profoundly changed the therapeutic management and prognosis of this hematologic disorder [1-3].

The IRIS (International Randomized IFN *versus* STI 571) study was a large international multicenter trial [3] on 1 106 patients (553 in each arm) treated in the chronic phase at diagnosis, included between June 2000 and January 2001. The STI (= Imatinib) group received a daily dose of 400 mg. The other arm was treated with the reference combination according to the usual posology: Interferon-alpha (IFC-alpha) in daily subcutaneous injection at progressively increasing dose up to 5 million units per day (in case of intolerance, the dose was reduced) combined with 20mg/m2 per day (maximum 40 mg) of cytosine-arabinoside (Ara-C) 10 days per month. Cross-over was planned in the event of intolerance or ineffectiveness. In terms of prognosis, there was no difference between the two groups in

terms for all important characteristics. The resulting publication, which is now the reference for this disease, provides the results after a median follow-up of 19 months. Imatinib became the first-line treatment for chronic-phase CML thanks to the IRIS study [2,3].

Chronic myeloid leukemia accounts for about 7-15% of adult leukemia according to published series. Its incidence in the world varies according to the countries, the lowest incidence is 0.7 found in Sweden and China and the highest is 1.7 found in Switzerland and the United States [4]. In Algeria, it was estimated at 0.4/100,000 inhabitants in 2004, and 0.46/100,000 in 2009, and its prevalence has been increasing worldwide since the advent of anti-tyrosine kinases [1,5].

It is the most common myeloproliferative disorder in Ouagadougou, accounting for 81.1% of myeloproliferative syndromes [6].

In the Department of clinical hematology of the YALGADO OUEDRAOGO University Hospital (CHU YO) in OUAGADOUGOU where all CML patients are referred, Imatinib (GIPAP®) is the standard treatment. Since 2004, the Glivec International Patient Assistance Program (GIPAP®), now Max Access Solutions (MAS), has been providing Imatinib (GLIVEC®), which is very expensive, free of charge for patients. The therapeutic strategy in CML has been disrupted by the introduction of Imatinib, a relatively specific inhibitor of BCR-ABL tyrosine kinase activity, which allows the normalization of the karyotype in more than 85% of cases and an overall survival estimated at 85% at 8 years according to the IRIS multicenter study. However, Imatinib gives the best results when the patient is in the chronic phase according to the IRIS study: in the chronic phase on Imatinib, the complete cytogenetic response is 41% compared to 17% in the accelerated phase and 7% in the acute phase [3].

The diagnosis and monitoring of Imatinib treatment of CML patients in BURKINA FASO are difficult to carry out because the key test, which is molecular biology (a quantitative polymerase chain reaction assay of the BCR-ABL transcript), is very expensive for the majority of our patients. Moreover, this molecular biology is carried out in France after venous blood collection in BURKINA FASO. Thus, in BURKINA FASO the majority of patients can't afford to perform molecular biology (RQ-PCR) every 3 months until confirmation of the major molecular response (decrease in the rate of BCR-ABL transcript >3 log or rate ≤ 0.1% compared to the initial rate) then every 6 months as recommended.

Since the introduction of Imatinib (GLIVEC®) in CML patients in OUAGADOUGOU, BURKINA FASO, there have been no studies to evaluate the management of patients treated with Imatinib for chronic myeloid leukemia at the YALGADO OUEDRAOGO University Hospital in OUAGADOUGOU, hence the interest of the present study. The overall objective of this study is to evaluate the management of patients treated with Imatinib for chronic myeloid leukemia at the YALGADO OUEDRAOGO University Hospital in Ouagadougou (BURKINA FASO).

Patients and Methods

This was a retrospective descriptive study based on the registers of consultations and hospitalizations of patients treated with Imatinib for CML in the Department of Clinical Hematology of the Yalgado OUEDRAOGO University Hospital, which is the reference center for CML management in BURKINA FASO. The study involved patients identified over 13 years from August 1, 2004, to July 31, 2017.

Any patient suspected of having CML and meeting one of the following conditions was included in the study:
- Presence of the Philadelphia chromosome in the hematological karyotype;
-and/or presence of the BCR-ABL fusion transcript at Fluorescence in situ after hybridization (FISH);
-and/or presence of the BCR-ABL transcript on molecular biology by RT-PCR (polymerase chain reaction using reverse transcriptase),
-CML patients who are treated with Imatinib (GLIVEC®).
Patients with less than three months on Imatinib (GLIVEC®) treatment were not included.

The criteria for exclusion

Any patient suspected of CML with an absence of both the Philadelphia chromosome and the BCR-ABL transcript.

The records of patients with CML were analyzed. The following parameters were collected: sociodemographic (age, sex, residence, occupation), clinical (personal and family history, clinical signs at diagnosis), biological (blood count, hematologic karyotype, cytogenetic and molecular tests), therapeutic (Imatinib, allopurinol), progressive (phases of CML, therapeutic response, disease progression, complications, death). The outcome of the patient (evacuated, monitored, deceased, discharged against medical advice) was specified.

The data collected were entered on a microcomputer and analyzed using statistical software sphinx version 4.5 and Excel 2007. The statistical test, Pearson Chi-square test was used to compare the variables. The difference was significant when the value was $p < 0,05$.

Operational definitions of terms

• Treatment failure: is the lack of improvement of the initial condition after treatment of at least 90 days;
• Lost to follow-up: any patient who has not returned in consultation for at least 3 months;
• Complete hematological response: corresponds to the normalization of the blood count;
• Complete cytogenetic response: corresponds to an absence of the Philadelphia chromosome in the analysis of the medullary karyotype;

- Partial cytogenetic response: Philadelphia chromosome (PH1): 1-35%;
- Minor cytogenetic response: PH1: 36-65%;
- Negligible cytogenetic response: PH1: 66-95%;
- Absent cytogenetic response: Ph1: ≥ 95%;
- Major cytogenetic response: Complete cytogenetic response + Partial cytogenetic response.
- Major molecular response: decrease in BCR-ABL transcript rate >3 log or rate ≤ 0.1% from initial rate;
- Complete molecular remission: BCR-ABL transcripts not quantifiable and not detectable on molecular examination.

Expected optimal response

- at 3 months: complete hematologic response and cytogenetic response
- at least a minor one;
- at 6 months: at least partial cytogenetic response;
- at 12 months: complete cytogenetic response;
- at 18 months: major molecular response but this response may continue to improve subsequently.

Sub-optimal response

- at 3 months: no cytogenetic response;
- at 6 months: lack of partial cytogenetic response;
- at 12 months: partial cytogenetic response;
- at 18 months: no major molecular response:
- and at any time, in the event of loss of major molecular response or mutation at low resistance levels.

In the failure of treatment

- at 3 months: no hematological response;
- at 6 months: no cytogenetic response;
- at 12 months: no partial cytogenetic response;
- at 18 months: no complete cytogenetic response;
- and at any time, in the event of loss of complete hematological response, or complete cytogenetic response, in the case of a high-level mutation of the resistance.

Good tolerance: Corresponds to normal transaminase values (ASAT, ALAT), total and direct bilirubin, uric acid, urea and creatinine during treatment; and the absence of cytopenias.

Bad tolerability: More than a three-fold increase in normal transaminases and more than a two-fold increase in bilirubin with cytopenias during treatment.

Results

Socio-demographic characteristics

During the period of our study, we identified 48 cases of confirmed chronic myeloid leukemia, which is an annual hospital recruitment rate of 3.7 cases. We identified ten (10) suspected but unconfirmed cases and nineteen (19) treated C.M.L. with less than three months of treatment duration.

There was a male predominance with a sex ratio of 1.52 (29 males/19 females). The mean age was 40 years (standard deviation=13.87) ranging from 13 to 80 years. The distribution by age group is characterized by a peak in frequency in the 40 to 50 age group with 16 cases /48 (33.3 %); and another peak between 30 and 40 years with 10 cases/48 (20.9 %).

The mean age was 40 years (standard deviation =13.87) ranging from 13 to 80 years.

The distribution of patients by sex shows 29 cases /48 (60.4%) for males and 19 cases/48 (39.6%) for females.

The male sex in the 40 to 50 age group was the most affected by the disease in 20.8% of cases. The characteristics of the distribution of patients by sex and age are specified in Table 1.

Age Sex	Less than 20 years	20 to 30	30 to 40	40 to 50	50 to 60	60 to 70	More than 70 years	Total
Male	3	3	8	**10**	3	2	0	29
Female	0	**6**	3	**6**	3	0	1	19
Total	3	9	11	16	6	2	1	48

Table1: Distribution of patients by sex and age

Housewives and farmers were the most affected by the disease. Table 2 illustrates the distribution of patients by socio-professional status.

Profession	Total	Frequency
Housewife	**14**	**29.1%**
Farmer	**9**	**18.7%**
Retailer	5	10.4%
Pupil	5	10.4%
Teacher	3	6.2%
Military	2	4.2%
Midwife	1	2.10%
Pharmacy assistant	1	2.10%
Veterinary assistant	1	2.10%
Driver	1	2.10%
Hairdresser	1	2.10%
Electrician	1	2.10%
Student	1	2.10%
Licensed nurse	1	2.10%
Warehouse clerk	1	2.10%
Koranic teachers	1	2.10%
Total	**48**	**100.0%**

Table 2: Distribution of patients by socio-professional status

Regarding marital status, there were 36 married /48 (75%), 10 single /48 (20.8%) and 2 patients abandoned by their partners because of their illness/48 (4.2 %).

The majority of patients, 28 cases /48 (58.3%) were living in rural areas.

Diagnostic aspects

The most common circumstances of discovery as shown in Table 3 were abdominal fullness, asthenia, and weight loss. Hearing loss and hemorrhage were the most common complications.

Circumstances of Discovery	Total	Percentage (%)
Abdominal fullness	**33**	**69**
Asthenia + weight loss	**9**	**19**
Adenopathies	6	12.5
Fever + cephalgia	6	12.5
Bone pain	5	10.4
Pallor	5	10.4
Hearing loss or Deafness	4	8
Hemorrhage	4	8
Abdominal pain	3	6.25
Decreased visual acuity	1	2
Thigh swelling	1	2
Priapism	1	2

Table 3: Distribution of patients by circumstances of discovery

In terms of functional signs, four patients/48 (8.3%) presented bone pain and six (12.5%) presented other functional signs, the most frequent of which were cephalgia.

The most common general signs were fever with three cases /48 (6.3%), asthenia in two patients /48 (4.2%) and weight loss reported in seven patients/48 (14.6%).

The most common physical signs were splenomegaly which affected 35 patients/48 that is 72.9% with 27/35 cases of type IV splenomegaly, 6/35 cases of type III splenomegaly and 2/35 cases of type V splenomegaly. The second most observed physical sign was hepatomegaly observed in 13 patients/48 (27.1%), followed by adenopathy observed in 6 patients/48 (12.5%); paleness was found in 5 patients/48 (10.4%) and finally, 3 patients/48 had edema of the lower limbs.

C.M.L. worsened in 8 patients/48 (16.7%), including 4 cases of hearing loss or deafness; 5 cases/48 of bleeding complications such as epistaxis, gingival hemorrhage, 1 case of hematoma of the thigh; 1 case of decreased visual acuity; 1 case of gout attack; 1 case of priapism.

Hyperleukocytosis ranged from 34.74 G/L to 661.90 G/L, with a mean white blood cell count of 246.21 G/L (standard deviation=150.44 G/L). The majority of patients, 35 patients /48 (72.9%), had a white blood cell count between 100 and 400 G/L. The mean neutrophil count was 129.87±87.38 G/L with the majority between 50 and 300 G/L.

Lymphocytosis was normal in 8 patients /48 while 40 patients /48 had hyperlymphocytosis, the majority of which was between 4 and 34 G/L.

None of the patients had normal monocytosis; 6 patients /48 had monocytopenia and 42 patients /48 had hypermonocytosis.

Only one patient had a normal eosinophil count, 7 patients /48 had eosinopenia and 40 patients /48 had eosinophilia.

The mean myeloblast count was 4.71 with extremes ranging from 0 to 19 per 100 white blood cells.

The number of promyelocytes was 0-23%; the average number was 3.29%.

The number of myelocytes ranged from 2 to 60.00% with a mean value of 24.06%.

With a mean count of 8.44%, there were 0 to 27 metamyelocytes per 100 white blood cells.

In our cohort, 38 patients /48 had anemia constituting 79.1% of the cases.

The mean hemoglobin level was 9.52g/dL with values ranging from 4.6 to 16.6 g/dL. Mild (10-12) or moderate (7-9.9) anemia was noted in the majority, i.e. 81.0% of cases.

In our cohort, there were 25 cases of normocytic anemia, 9 cases of microcytic anemia and 7 cases of macrocytic anemia. Seventeen patients had a normal mean corpuscular hemoglobin concentration (MCHC).

The mean platelet count was 391.4G/L (83-1079G/L), 16 patients /48 had thrombocytosis and 5 patients /48 had thrombocytopenia.

On the myelogram, the bone was 100% normal in hardness with a myeloid hyperplastic rich marrow prevailing over the granular lineage with no maturational hiatus.

For the confirmation of the diagnosis, 35 patients /48 (72.9%) of the patients had to undergo karyotype which showed the presence of the Philadelphia chromosome in all of them.

Four (04) patients had additional chromosomal abnormalities including two duplications of the Philadelphia chromosome, one trisomy 8 and a combination of the two.

FISH was performed in 22 patients /48 (45.8%). The BCR/ABL transcript was detected in all of them; of which five (5) had a double fusion and five (5) also had a deletion of ABL.

The molecular biology by RT-PCR was performed in 12 patients /48 (25%). The BCR-ABL rearrangement was found in all of them at a percentage of more than 70%.

HIV serology was negative in all patients.

HBV serology: HBsAg was found in seven patients while anti-HBc was found in 11 patients.

HCV serology: The Anti-HCV antibody was found in one patient.

Concerning the progressive phases, 39 patients /48 were diagnosed in the chronic phase compared to 9 patients /48 in the accelerated phase.

Therapeutic aspects

The Initial Daily Dose of Imatinib was 400mg in 38 patients/48 (79.2%), 600mg in 9 cases/48 (18.7%) and 300mg in one patient (child) or 2.1%.

The dose of Imatinib was systematically increased in the case of disease progression and decreased in the event of intolerance.

As a preventive measure, all patients were prescribed Allopurinol 300 mg/day once a week.

The Sokal score was calculated in 22 patients: 59.09% of these patients were classified as high risk. Table 4 shows the distribution of patients according to the Sokal score.

SOKAL score	Total	Percentage
High risk	**13**	**59.1**
Intermediate risk	6	27.2
Low risk	3	13.7
TOTAL	**22**	**100**

Table 4: Distribution of patients according to the Sokal score

After three (03) months of treatment with Imatinib, there were no side effects in 37 patients /48 (77.1%). In 11 patients/48 (22.9%) who had side effects, the most frequent was depigmentation which was reported in five cases/48 (10.4%), followed by nausea, abdominal pain, water and salt retention, and joint pain.

One case of diarrhea and skin rashes was noted at 12 months of treatment.

After two (02) years of treatment, there were three cases of hydro-sodium retention (edema of the lower limbs, weight gain), three cases of abdominal pain, two cases of vomiting, muscle cramps, headaches, and depigmentation, and one case of myalgia and joint pain.

The side effects that persisted after three years of treatment included muscle cramps, joint pain, and sodium retention.

Joint pain, skin rashes, and muscle cramps persisted up to the fifth year of treatment in some patients.

After eight years of treatment, one case of muscle cramps was reported.

After three months of treatment, 30 patients/48 (62.5%) of the patients presented cytopenias, of which 27 cases /30 (90%) were anaemia, 10 cases /30 (33.3%) thrombocytopenia, and 11 patients/30 (36.7%) presented leuko-neutropenia.

Of the 46 still undergoing treatment, 22 still had cytopenia at one year of treatment, broken down as follows: 18 cases/22 (81.8%) of anemia, ten cases /22 (45.4%) of thrombocytopenia and six cases/22 (27.3%) of leuko-neutropenia.

There were 19 cases of cytopenias including 16 cases of anemia, seven cases of thrombocytopenia and five cases of leuko-neutropenia at two years of treatment.

After three years, there were ten cases of cytopenias including nine cases of anemia, five cases of thrombopenias and two cases of leuko-neutropenias.

There were ten cases of cytopenias including eight cases of anemia, three cases of thrombopenias and four cases of leuko-neutropenias at five years.

At three months of treatment, 25 patients /48 (52.1%) had achieved complete hematologic remission (CHR).
At one year of treatment, 24 cases /48 (50.0%) had achieved CHR.
At two years of treatment, 31 cases/48 (64.5%) had achieved CHR, only one patient/48 (2.1%) had no CHR.
HCR was achieved in 33 cases /48 (68.7%) at 3 years of treatment.
HCR was reached in 25 patients /48 (52.1%) at five years, which is less as compared to three years; 8 patients lost their HCR.
After the first five years, the HCR was 100% complete.

Of the two patients who had undergone cytogenetic testing at one year of treatment, one patient achieved minimal cytogenetic remission and the other achieved partial remission.

At two years of treatment, of the two patients who had undergone cytogenetic testing; one achieved complete cytogenetic remission, and the other had minimal cytogenetic remission.

Cytogenetic remission could not be assessed at three years of treatment because no cytogenetic testing was performed at that time.

There was one case of complete cytogenetic remission at 5 years of treatment.

Three patients were able to undergo molecular testing, none of whom had achieved molecular remission in two years.

There was no complete molecular response (CMR) at three years of treatment as the patient who underwent the molecular monitoring still had 11.1% of the BCR/ABL rearrangement.

Molecular monitoring in two patients at five years of treatment showed a major molecular response (MMR).

At eight years of treatment, there was a CMR and MMR; at eleven years a CMR.

In summary, an optimal response was obtained in three patients; one suboptimal response in seven patients and one failure.

A total of three cases of resistance were reported, two of which were detected at two years of treatment and one at three years, due to patient's discontinuation of the drug.

The outcome of the patients was marked by 39 patients/48 (81.2%) who were still being monitored. Table 5 presents the characteristics of the patients' outcomes.

	Still monitored	Deceased	Lost to follow-up	Total
Total	**39**	6	3	48
Percentage (%)	**81.25**	12.5	6.25	100

Table 5: Patients' outcomes

Discussions

Constraints and limitations of the study

Selection bias: patients treated in private clinics or by traditional medicine were excluded. Nineteen (19) confirmed cases of MCL treated with Imatinib in less than three months were not included because the progression was assessed from three months onwards.

Information bias: sources of information bias included the incompleteness of data in the patient's medical record and the difficulty in obtaining information on the medium- and long-term outcomes which are characteristics of retrospective studies.

Confounding bias: The failure to perform some specialized paraclinical examinations that can detect co-morbidity and modify the course of the hematologic malignancy may be a confounding factor.

The major constraint of our study was the difficulty related to the financial and geographical availability of:

-CML confirmatory examinations (karyotype, FISH, molecular biology) for the diagnosis of C.M.L. The karyotype was carried out on 35 patients/48, the FISH was carried out on 22 patients/48 and the molecular biology on 12 patients/48.

-The key therapeutic monitoring test (molecular biology by the R-T PCR). Only three patients were able to undergo molecular testing.

The lack of treatment of our MCL patients who required treatment with second-line tyrosine kinase inhibitors (nilotinib, dasatinib) was a detrimental factor in the prognosis.

Socio-demographic characteristics

In 13 years, 48 cases of CML were collated with an annual incidence of 3.7 cases.

Segbena *et al.* [7] in Togo found 5.8 cases in 2012, Ngock *et al.* [8] in Cameroon observed 6.08 cases per year in 2016. Difficulties in operating the Glivec program (GIPAP) might explain our low annual incidence rate. From 2004 to 2011, there were only three patients with Chronic Myeloid Leukemia treated with Imatinib (GLIVEC®). A slight male predominance was found in our series with a sex ratio of 1.52. The same finding was reported by several african authors [7-9]. Although some authors report a slight female predominance [10], male predominance is classically observed in the literature and CML is thought to affect both sexes equally. The mean age at diagnosis was 40 years ranging from 13 to 80 years. The mean age found in our study is similar to those of Segbena *et al.* [7] in Togo, Ngock *et al.* [8] in Cameroon who found 40.52 years (9-72); 41 years (15-68) respectively. Gaudong *et al.* [11] in a study in Gabon found an average age of 36.5 years (ranging from 21-62), which is slightly lower than ours. Erius *et al.* [9] found an average age of 43 years (11-84) in Tanzania, Hagop *et al.* [12] in Texas (USA) found an average age of 48 years (15-79), which is higher than ours. These results suggest that CML remains a condition of young adults. In our cohort, the most affected by the disease were housewives and farmers. Our results could be explained by the fact that housewives and farmers are the most numerous socio-professional categories in Burkina Faso. Gaudong *et al.* [11] in Gabon noted that the most affected by the disease were patients with high-risk occupations: chemists and mining company employees.

Clinical aspects

The most common circumstances of discovery in our study were abdominal fullness, asthenia, and weight loss. Symptoms/signs presented by patients at diagnosis were diverse and consistent with those described in the literature. Thus, abdominal fullness was found in 69% of cases, asthenia and weight loss in 19% of cases. The other symptoms/signs were fever and headache (12.5%), bone pain (10.4%), pallor (10.4%), abdominal pain (6.25). These results are similar to those of Erius *et al.* in Tanzania [9].

Clinically, the number of patients with splenomegaly in our study 72.9% was comparable to that reported by several african authors [7,8,11]. Other authors including Sanogo *et al.* [10] reported 100% splenomegaly. The analysis of our results led us to note that splenomegaly was generally of Hackett's type III, IV, V with a predominance of type IV, i.e. 77.4% of cases. Sanogo *et al.* [10] in a study conducted in Côte d'Ivoire reported that Hackett's type IV splenomegaly was the most prevalent (27.5% of cases), then type III and type V (25% and 25%) at the time of diagnosis. As a result, cases of CML without an enlarged spleen are unusual. In these cases, an ultrasound scan reveals splenomegaly that is not palpable. Hepatomegaly was present in 27.1% of our patients. Sanogo *et al.* [10] and Segbena *et al.* [7] found 20% and 28% respectively. The difference in results between authors could be explained by the fact that ultrasound, which could find hepatomegaly not perceptible on palpation, was clinically sought by some authors while others appreciated it by ultrasound, which is more sensitive.

Biological aspects

In our study, the mean leukocytosis was 246.21 G/L (standard deviation = 150.44), ranging from 34.74 G/L to 661.9 G/L. Gaudong *et al.* [11] in Gabon and Erius *et al.* [9] in Tanzania found mean leukocyte values of 182G/L and 224G/L respectively. Comparing our results with data from the French literature, it can be noted that the mean leukocytosis in France, which was 120 G/L (8 to 500 G/L) [13], is lower than that observed in our series. According to Guilhot *et al.* [13], this could be explained by the fact that the disease is being diagnosed more and more frequently in France following a systematic haemogram performed during a health check-up. In Africa, in general, and in our series in particular, early forms are rare and might result from the under-medicalization of Burkina Faso. The average hemoglobin value was 9.5g/dL with values ranging from 4.6 to 16.6 in our series and anemia was present in 81% of cases. Segbena *et al.* [7], Gaudong *et al.* [11] and Erius *et al.* [9] found mean hemoglobin values of 10.57, 9.5 and 8.5g/dL respectively.

The fluctuation in sample size which was 17 cases in Gabon for Gaudong *et al.*, 25 cases in Togo by Segbena *et al.* and 127 cases in Tanzani for Erius et al could explain the variation in mean hemoglobin levels found in these different studies. The number of platelets varied between 83 and 1079 G/L with an average of 391.39 G/L in our patients. We observed thrombocytopenia in six patients/48 (12.5%) and hyperplaquettosis in 19 patients /48 (39.6%). In CML, platelet counts are usually normal, rarely decreased [9-11].

Progessive aspects

At the time of diagnosis 39 patients /48 (81.3%) of our patients were in the chronic phase and 9 patients/48 (18.7%) in the accelerated phase. Most authors [8,11,14,15] had similar results to ours. Consequently, CML is most often diagnosed in the chronic phase. The prognosis of our patients, as assessed by the Sokal score, was high risk for 28 patients /48 i.e. 58.3%, moderate risk for 13 cases /48 (27.1%) and minor risk for seven patients/48 (14.6%). Gaudong *et al.* [11] in Gabon found high risk in 41% of cases, intermediate risk in 30% and low risk in 29% of cases. Philippe Rousselot *et al.* [15], on the other hand, found low risk in five patients/12 (41.7%), intermediate risk in five cases /12 (41.7%) and high risk observed in two patients/12 (16.6%). In Africa, the majority of CML is diagnosed with a high Sokal score revealing a delayed diagnosis for the majority of our patients and a lack of medical staff and technical resources. The insidious progression of CML is a cause of delayed consultation. In contrast, Philippe Rousselot *et al.* in France [15] found a low risk for five patients/12, an intermediate risk for five patients/12 (41.7% of cases), and high risk in 8.33% of cases.

From the third month of treatment, hematologic remission during treatment ranged between 50 and 100%. Between the second and third year of treatment, 17% of patients had lost their complete hematologic response. Ngock *et al.* [8] in Cameroon found 96% complete hematological remission on average at 1.8 months, 12% of which was lost during treatment for an average of 7 months. Segbena *et al.* [7] had achieved 80% complete hematological remission after an average of 3 months of treatment with two cases of loss of complete hematological remission. Besides, patients who were started on Imatinib had better hematologic remission [8]. This difference in results may be explained by the fact that some of our patients had received Hydroxyurea before the introduction of Imatinib.

Molecular monitoring by RQ-PCR made it possible to assess patient progress. Of our patients who underwent the reassessment, 22% had achieved complete molecular remission, 33% achieved major molecular remission and 44% had no remission after five years of treatment. Many of our patients were unable to do residual disease control (molecular biology) due to a lack of financial means. Higher remission rates have been reported by other authors: Segbena *et al.* [7] reported 48% complete molecular remission; Gaudong *et al.* [11] reported 40% major molecular remission. The fact that the majority of patients who underwent the control were those in whom no favorable progression through hematologic response was observed might explain the difference in results in our series. The delayed diagnosis of our patients could also explain our results as the majority of our patients (58.3%) have a high-risk Sokal score.

About hematologic side effects, progression was favorable during the treatment and after the first five years, eight cases of anemia, three cases of thrombocytopenia and four cases of transient leuko-neutropenia were observed in our study. These cytopenias were also reported by several authors [7].

The non-hematologic adverse effects included skin discoloration followed by weight gain, abdominal pain, nausea, vomiting and diarrhea, muscle cramps and skin rashes. All these complications, described by several authors, were transient and disappeared with symptomatic treatment. Most of the authors had described the usual side effects, which are: weight gain, edema, nausea, vomiting, and muscle pain. A few European authors had described unusual skin side effects on Imatinib, such as skin pigmentation disorders.

In our study, the therapeutic response could be assessed in only 11 patients /48. Of these, three patients /11 i.e. 27.3% achieved an optimal response, seven patients/11 (63.7%) achieved suboptimal response and one/11 (9.1%) had failed within five years of treatment. These results are similar to those obtained by Segbena *et al.* [7]. This could be explained by the occurrence of secondary resistance (by tyrosine kinase domain mutations). Three cases of resistance were detected in our study. The occurrence of secondary resistance to Imatinib requires regular molecular monitoring so that it can be detected early to preserve the prognosis and survival of patients. It will be challenging to carry out regular molecular monitoring considering the current technical facilities and the poverty of the majority of our patients.

In our study, we noted six deaths /48 patients (12.5%) with 92.34% five-year survival and 6.25% lost to follow-up. There were blast transformations after rapid acceleration despite Imatinib treatment and dose increase. Our rate of lethality is similar to the other african authors [9,11,12]. The lack of adequate means to manage blast transformation, or even hematological complications requiring resuscitation in a specialized unit might explain the death rates.

Conclusion

CML is a pathology present in our context and it affects all segments of the population with a slight prevalence in men. The most affected patients are farmers and housewives. Clinically, splenomegaly is quite frequent but the positive diagnosis is primarily based on hematologic information (CBC), cytogenetics (caryotype, Fluorescence In Situ Hybridization) and molecular biology. The natural progression of the disease goes through three phases: chronic, accelerated and blastic.

Thanks to the advancements in the management of CML, transitioning to advanced phases is increasingly delayed. Several patients remained in remission for a longer time. In early 2000, the discovery of kinase tyrosine inhibitors has transformed the management of CML patients, and Imatinib has become the first-line treatment for CML in the chronic phase. Despite the treatment, progressive complications and secondary resistance still occur.

Acknowledgment

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